



Better Health
Through Responsible
Self-Medication

NONPRESCRIPTION DRUG MANUFACTURERS ASSOCIATION

September 4, 1998

~~B7E, HHS, CSEP, to F-013-58~~

Food and Drug Administration
Dockets Management Branch
Room 1061, HFA-305
5630 Fishers Lane
Rockville, Maryland 20852

Re: Docket No. 98N-0339

Dear Sir or Madam:

Pursuant to section 406(b) of the FDA Modernization Act (FDAMA), the Food and Drug Administration (FDA) is required to consult with its external stakeholders, identified in FDAMA as "appropriate scientific and academic experts, health care professionals, representatives of patient and consumer advocacy groups, and the regulated industry." Following these consultations, FDA is to publish a plan for achieving compliance with each of its obligations under FDAMA. To this end, FDA has requested comments to a list of questions regarding how the agency can best meet six objectives of its modernization plan (see *Federal Register* 63: 39877-39879, July 24, 1998).

The Nonprescription Drug Manufacturers Association (NDMA) is the 117-year old trade organization representing the manufacturers of nonprescription drugs and over-the-counter (OTC) dietary supplements. By sales, NDMA members represent over 95% of the OTC drug marketplace. NDMA has been very active in its interactions with the agency on such matters as OTC drug approval, safety and effectiveness, and labeling issues and matters affecting the manufacturing and packaging of quality OTC self care products.

NDMA submits these comments that focus on certain of the questions posed by the agency in the July 24, 1998 *Federal Register* notice.

First, FDA asks: What can FDA do to improve its explanation of the agency's submission review processes, and make explanations more available to product sponsors and other interested parties?

NDMA urges continued emphasis on outreach by each Center. Industry groups specialize according to product types, as does FDA (e.g., food, drugs, devices, biologics, veterinary medicine). Trade organizations and other outside groups, such as the Food and Drug Law Institute (FDLI), Drug Information Association (DIA) among others, hold regular meetings on topics of current importance. FDA's involvement in the planning and presentation of evolving

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review processes affecting the members of the various trade associations is extremely important as a means of ongoing mutual education.

In addition, several years ago, NDMA suggested to CDER Review Management that key personnel in the agency prepare and/or publish procedural and interpretive explanations of their spheres of operations. For example, Mr. D. Boring published an in-depth article in *Pharmaceutical Executive* on the operations of CDER's Nomenclature Committee. While prior to that publication we received many comments from our members concerning the nature and specifics of this CDER Committee, once light was shed on the matter, industry better understood the how and why of the agency's decisions, thereby helping not only to reduce the frequency of such questions but also – more importantly – to smooth mutual interactions between FDA and industry in the drug approval process.

Another example relates to a "Points to Consider" paper that was issued by Dr. Debra Bowen several years ago at a Nonprescription Drugs Advisory Committee (NDAC) meeting. The paper pertained to the agency's informal thinking on the matter of the purpose and design of actual use studies, which had become by that time pivotal to many Rx-to-OTC switch applications. While the "Points to Consider" paper was not a formal guidance, it represented the agency's current thinking and was helpful to companies as a spring board to developing R&D plans and in discussions with the agency on protocols. Such in-depth publications or informal "Points to Consider" can be advantageous to both FDA and industry, in that they can not only prompt the authors (i.e., agency personnel) to focus critically on their own sphere of influence and operations, but also allow industry a better chance to evaluate the process and offer constructive suggestions. Such formal and informal publications are not intended to take the place of more formal guidelines or guidances, but they can serve as effective sounding boards to elicit discussions that ultimately improve how we undertake our respective roles in drug development. NDMA urges FDA continue to encourage such activities.

However, while NDMA strongly supports FDA's interest in improving its explanation of the agency's submission review processes, NDMA believes that FDA should continue to seek ways to further enhance the efficiency and speed of the review processes themselves. User fees are a singularly important development in reducing review times for new drugs in recent years; nevertheless, it is still important for both industry and FDA to seek ways to achieve further refinements of the system. Such refinements are best identified through ongoing dialogue between industry and FDA. That can be achieved in a number of different ways, e.g., FDA-sponsored open meetings, meetings with trade and professional associations, etc. Such meetings have been, and are, used by FDA and industry, and NDMA provides strong encouragement that they continue and continue to receive a high priority among CDER personnel.

Second, FDA asks: what approach should the agency use to assure an appropriate scientific infrastructure with continued access to the scientific and technical expertise needed to meet its statutory obligations and strengthen its science-based decision making process?

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NDMA has several recommendations in this area pertaining to on-going joint education of agency personnel and the agency's use of outside experts.

First regarding on-going education, NDMA believes that a partnership-type interaction between the agency and industry is a highly-valued and important approach to ensuring FDA's drug reviewers and compliance personnel have continued access to evolving scientific and technical advances in the field of self care. For example, such interaction can be accomplished through current approaches to joint training of FDA inspectors and industry personnel involved in Manufacturing Controls Processes, and NDMA encourages the agency to continue to give priority to this type of activity.

Second, we suggest that a regularly scheduled OTC update meeting be jointly sponsored by FDA's Division of OTC Drug Products and NDMA. This meeting, perhaps held annually or biannually, would focus on matters that FDA and NDMA have mutually identified as aspects of "OTCness" about which any OTC regulator should be familiar in order to contribute to well-rounded, well-informed, reasonable, and fair public health decisions about the products that they regulate. NDMA is willing to organize industry experts to describe the latest advances and practices of the OTC industry pertaining to, for example, packaging (child- and tamper-resistant packaging, elder friendly packaging, labeling (e.g., full label shrink over-wrap printing, etc.), manufacturing practices, adverse experience reporting systems, application of toll-free consumer service programs, methodologies for label comprehension and actual use and other clinical studies, etc. These sessions could be organized as tutorials, and an ongoing educational credit system within FDA could be developed as part of career development in the OTC product sector. Such sessions could be an extremely useful way to broaden the perspective of OTC drug reviewers and managers on the capabilities of the industry they regulate.

FDA's acceptance of this offer is dependent on the agency being committed to the proposition that a dynamic learning environment creates informed individuals who are better motivated and better equipped to make well-reasoned, scientific and regulatory judgments for the benefit of the consumer. FDA may wish to consider such meeting with trade associations in other product sectors.

Third, with respect to FDA's use of outside experts, the agency has used the advisory committee process as an integral part of its scientific decision-making relating to drug approval and review. NDMA supports this approach, and in fact was instrumental in helping to establish the Nonprescription Drugs Advisory Committee in 1992. NDMA urges FDA to continue to place emphasis on the orientation of new advisory committee members. NDMA has been involved in orientation sessions for the Nonprescription Drugs Advisory Committee members as well as new members to prescription drugs advisory committees. These sessions have been highly useful as a means of sharing the industry's perspective of OTCness. We encourage that this attain an on-going high priority as an ongoing program within CDER and other centers.

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Third, FDA asks: what other objectives related to the agency's statutory obligations or public expectations--beyond the six objectives--should be included in the FDA plan?

Rx-to-OTC switch is vital to the future of self care and the OTC industry. Not only is switch the principal reservoir for future novel self care therapeutics for the consumer, it is critical to the US health care system overall. The cost savings to the health care system due to Rx-to-OTC switches are well documented.

So that the Rx-to-OTC switch process itself remains vital and productive in the future, decisions on a switch candidate's OTCness should be made on a data-driven, case-by-case basis through an OTC benefit/risk assessment undertaken by FDA in partnership with the sponsor and, as needed, the appropriate CDER advisory committees.

OTCness encompasses a broad array of factors affecting consumer use of nonprescription medicines. It is defined as "... the widespread availability of safe and effective nonprescription medicines for responsible self care by the consumer according to label directions, pursuant to the applicable laws, regulations, and voluntary industry codes affecting manufacturing, packaging, labeling, distribution, and sales of quality products and the advertising of those products in all media." [Soller, R. W.: OTCness. *DIA Journal* 32: 555-560, 1997.] The pivotal decision in determining widespread availability of OTCness is the OTC benefit-risk assessment. [U. S. Government: 21 *Code of Federal Regulations* 330.10(a)(4)(iii).]

Under the FD&C Act, any drug which cannot safely be used without medical supervision must be labeled for sale and be dispensed only by prescription of a licensed practitioner, otherwise it is OTC. 21 USC § 353(b)(1). Hence, by law, drugs are prescription by exception. In other words, as concluded by a former FDA General Counsel, if it can be OTC, it must be OTC. [Hutt, P.B.: A legal framework for future decisions on transferring drugs from prescription to nonprescription status. In: Proceedings of the NDMA Symposium "Rx OTC: New Resources in Self Medication," November, 1982.]

To meet this legislative underpinning of OTCness, FDA has adopted a case-by-case, data-driven process through the OTC Review rulemaking to define the OTC benefit-risk assessment. Each novel Rx-to-OTC switch has been characterized by a full array of data including, depending on the specific switch, studies relating to postmarketing surveillance of the Rx parent, postmarketing surveillance of foreign marketing experience, dose ranging studies, long term safety studies, OTC actual use studies, label comprehension studies, specialized safety studies in enriched patient populations, and even Rx actual usage studies (i.e., undertaken for comparison purposes with OTC actual usage studies).

Thus, the regulatory dialogue in the R&D phase of Rx-to-OTC switch has been characterized by companies defining study designs to answer specific questions about a switch candidate's safety or effectiveness in the prospective OTC setting. Because the law is in effect biased for OTCness, FDA has typically not foreclosed whole categories of self-care therapeutics, until one case very

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recently. In 1997, FDA issued a negative guidance on OTC drugs for the treatment of hypercholesterolemia, stating:

“...(a) health care practitioner supervision in the diagnosis and ongoing management of hypercholesterolemia is essential for safe and effective use of drug products to treat this condition and (b) this supervision is assured within the context of prescription access to the appropriate drug(s) for the individual patient. CDER therefore believes that drugs for the treatment of hypercholesterolemia should not be sold OTC in the United States.” [Food and Drug Administration: Guidance for Industry on OTC Treatment of Hypercholesterolemia. *Federal Register* 62: 55645-6, 1997.]

This type of negative guidance runs counter to the long history of a case-by-case, data-driven approach to Rx-to-OTC switch. It would have been more appropriate for FDA to issue a document elaborating the specific questions that would have to be answered were a decision be made favoring OTCness for drugs to treat hypercholesterolemia. Indeed, it is incongruous in today's environment of dietary supplement claims for maintaining a healthy cholesterol (i.e., maintains a healthy lower cholesterol) and cholesterol-lowering health claims for psyllium food products that FDA would discourage a data-driven process to support an OTC claim in the same therapeutic/health promotion category. Indeed, the actual use study on cholestyramine supported its safety and effectiveness in an OTC setting (i.e., it was comparable to the Rx profile).

In sum, FDA's recent negative guidance on OTC hypercholesterolemia products and the prior history of Rx-to-OTC switch defined in recent times by the actual use study demand that industry and FDA insist that data drive the decision for the OTC benefit-risk assessment. This means that the specific questions that need to be answered through data development are carefully defined by through dialogue between companies and FDA, and if an OTC decision can still not be made, then the agency should articulate the outstanding questions. In this way, as consumers become even more sophisticated about self-care and/or new potential OTC therapies appear on the OTC horizon, the door remains open – for the ultimate benefit of the consumer. The future of OTCness depends on dialogue, respect, and a mutual desire to seek the best possible therapeutic options for Americans in an overall public health context, even if it means breaking traditional concepts of drug therapy.

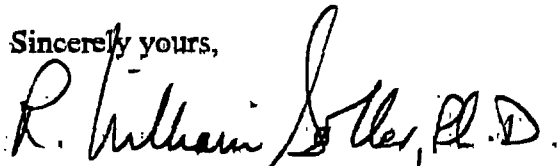
NDMA therefore recommends that FDA reissue the Guidance on Hypercholesterolemia (see *Fed. Reg.* 62: 55645-6, October 27, 1997), omitting a declaration that this category is “off limits” to potential future Rx-to-OTC switch products and defining the specific outstanding questions that are to be answered satisfactorily in order to define OTCness for a class of products that lower cholesterol levels.

In conclusion, NDMA's comments derive from the Association's long-standing commitment to the view that, from standpoints of public safety and management efficiency, the development and regulation of OTC self care products are best undertaken when regulators and the regulated

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share a goal of mutual cooperation and partnership. NDMA has in the past made suggestions on how to achieve this goal, as we do here, and as we will continue to do in the future.

Sincerely yours,

A handwritten signature in black ink, appearing to read "R. William Soller, Ph.D.", written over the typed name.

R. William Soller, Ph.D.
Senior Vice President and
Director of Science & Technology

WS/jkq/FDAMA/CDERCOMFDAMA.WORD